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10/693,252

10/24/2003

Thomas J. Meade

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EXAMINER

SCHLIENTZ, LEAH H

ART UNIT

PAPER NUMBER

1618

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|-------------------------------------|--|
| Office Action Summary | Application No. 10/693,252 | Applicant(s) MEADE ET AL. | |
| | Examiner Leah Schlientz | Art Unit 1618 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-23 and 26-36 is/are pending in the application.
- 4a) Of the above claim(s) 26-28 and 30-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-23, 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/5/2009 has been entered.

Status of Claims

Claims 19 and 20 have been amended. Claims 24 and 25 have been cancelled. Claims 19-23 and 26-36 are pending, of which claims 26-28 and 30-36 are withdrawn from consideration at this time as being drawn to non-elected species. Claims 19-23 and 29 are readable upon the elected invention and are examined herein on the merits for patentability.

Priority

It is noted that the instant Application claims benefit of US Provisional Application 60/421,470, filed 10/24/2002, and is a continuation-in-part of US 09/715,859, now US 6,673,333, filed 11/17/2000, which claims benefit of US Provisional Application 60/201,816, filed 5/4/2000. However, upon examination of the priority documents, it is

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noted that the first recitation of the structure now claimed in claim 19 having variables X_1 , Y_1 , Y_2 , n and m defined as claimed, and the structure in claim 20 having variables X_1 , X_2 and p defined as claimed, is in the instant specification. Therefore, for the purposes of prior art search, the effective filing date of the pending claims is interpreted to be the filing date of the instant Application, 10/24/2003.

Response to Arguments

Applicant's arguments, with respect to the rejection of claims 19 and 21 under 35 USC 112, first paragraph, have been fully considered but they are moot in view of new grounds for rejection set forth hereinbelow.

Applicant's arguments, with respect to the rejection of claims 20, 22 and 29 under 35 USC 102(e) as being anticipated by Lauffer (US 6,709,646), have been WITHDRAWN as being overcome by amendment.

Applicant's arguments, with respect to the rejection of claims 19-23 and 29 under 35 USC 103(a) as being unpatentable over Lauffer (US 6,709,646) in view of Netzel-Arnett (*Biochem*, 1993, 32, p. 6427-32), have WITHDRAWN as being overcome by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method, comprising administering an MRI agent having the formula: a metal DOTA chelate conjugated to $X_1-(Y_1)_n\text{-Ala-Leu}-(Y_2)_m$, where Y_1 and Y_2 are independently amino acid moieties, and n and m are independently an integer from 0 to 5. Such a peptide sequence results in literally millions upon millions of potential sequences (i.e. each Y_1 and Y_2 may independently represent 20^5 structures, not to mention the exponential number of possibilities of sequences which result from their various combinations). However, applicant has provided examples of only a few representative peptide sequences which correspond to the claimed genus (i.e. SEQ. ID 1 – 4, as well as the sequences provided in Example 1, paragraphs 243 – 270). Such a limited disclosure of a few representative species does not provide support that applicant has possession of a reasonable number of species of the claimed genus to substantiate claiming such a broad genus which may include millions and millions of potential species.

The specification does not appear to provide support that a reasonable number of species within the claimed genus would be capable of achieving the claimed activity such that upon administration of the compound that an increase in the q value of the

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MRI agent would be achieved. For example, Netzel-Arnett *et al.* (*Biochem.*, 1993, 32, p. 6427 – 6432) describe that matrilysin, or PUMP-1 (i.e. MMP-7) hydrolyzes proteoglycans, fibronectin, laminin, gelatin and other substrates (page 6428, left column), and teaches that a homologous MMP family of proteinases can exhibit diversity in their protein substrate specificity. Netzel-Arnett studied the **sequence specificity of PUMP** in order to elucidate the contribution of sequence specificity to protein specificity, important to the design of optimized synthetic substrates and inhibitors (page 6428, left column). Peptides 1 – 58 were prepared and compared to a reference octapeptide which is modeled after the collagenase cleavage site of calf/chick alpha1(1) chain of collagen. **Kinetic parameters for the hydrolysis of these peptides by PUMP** was determined (page 6428). It is acknowledged that PUMP exhibits a strong preference for Leu in subsite P₁' of a representative peptide (page 6431, left column and Table 5). However, Netzel-Arnett also teach that other substitution may lead to reduced or abolishment of hydrolysis activity. See page 6429, left column, where truncation of a peptide sequence, such as in peptide 9, abolishes activity. Subsites P1, P2, P3, P4, P1', P2', P3', P4' all show varying effects on hydrolysis rates upon substitution, some of which lead to significant decrease or undetectable rates of hydrolysis (pages 6429-6431). Therefore, based on the apparent requisite substrate specificity required by the PUMP enzyme, it does not appear that Applicant has not provided a reasonable number of species to support such a broad genus of peptide sequences, since amino acid substitution in a variety of subsites may lead to inactivity towards hydrolysis. It is unclear from the specification if other enzyme

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systems are capable of acting upon the claimed compounds having the genus of peptide sequences claimed. Since hydrolysis appears to be necessary for increasing q value of the contrast agent, various amino acid substitutions in the peptide sequence could lead to inactive compounds. Applicant has provided examples of only a few representative peptide sequences which correspond to the claimed genus, however, such a limited disclosure of a few representative species does not provide support that applicant has possession of a reasonable number of species of the claimed genus to substantiate claiming such a broad genus which may include millions and millions of potential species, thus, not providing a structure/function relationship between the possible sequence and the function thereof. "A patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." *Noelle v. Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004). Applicant has not provided support to show that a reasonable number of species from within the claimed genus would be capable of providing an increase in q value of the MRI agent upon administration of the agent, based on the apparent unpredictability in the protein substrate specificity of PUMP.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-23 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Meade *et al.* (WO 02/080757, whereby US 2003/0021750 is relied upon as equivalent).

Meade discloses metal ion complexes comprising a chelator structure and a blocking moiety which may be covalently attached to the chelator structure (paragraph 0031). Suitable MRI contrast agents have the formula shown in structure 1, Fig. 1. M is a paramagnetic metal such as Gd(III). See DOTA chelators Figure 4. The X moiety (sometimes referred to herein as the "core"), can be any chemical moiety that allows the functional connection of the "arms", e.g. the moieties comprising the coordination atoms and/or the coordination site barriers. In general, X comprises an alkyl or aryl moiety (paragraph 0034). In a preferred embodiment, the chelator structure and the blocking moiety are covalently linked; that is, the blocking moiety is a substitution group on the chelator structure. In this embodiment, the substituted chelator structure, with the bound metal ion, comprises the metal ion complex which in the absence of the target substance has all possible coordination sites occupied or blocked; i.e. it is coordinatively saturated (paragraph 0066). What is important is that the metal ion complex, comprising the metal ion, the chelator structure and the blocking moiety, is not readily able to rapidly exchange water molecules when the blocking moieties are in the inner coordination sphere of the metal ion, such that in the absence of the target substance, there is less or little substantial image enhancement (paragraph 0068). The blocking moiety has a functional moiety which is capable of interacting with a target substance (paragraph), for example the blocking moiety will stop blocking or occupying at least

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one coordination site of the metal ion complex when the target substance is present (paragraph 0071). In a preferred embodiment, the target substance is an enzyme, and the blocking moiety is an enzyme substrate (paragraph 0075). The blocking moiety comprises a tumor associated activable guarding moiety ("TAAGM") (paragraph 0094), which is an MMP in a preferred embodiment (paragraph 0113). Examples of target substance/peptide blocking moiety pairs include MMP-7 and PMALWMR (paragraph 0149). In the presence of the enzyme target, the enzyme cleaves one or more of the enzyme substrates, either within the substrate or at the point of attachment to the metal ion complex, thus freeing the coordination site barrier. The coordination site or sites are no longer blocked and the bulk water is free to rapidly exchange at the coordination site of the metal ion, thus enhancing the image (paragraph 0145). Absent evidence to the contrary, such a mechanism would inherently increase q value, as claimed, since q value is the number of water molecules associated with a metal complex.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 20, 22 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade *et al.* (US 5,707,605) in view of Lauffer *et al.* (US 6,709,646).

Meade discloses MRI contrast agents comprising a paramagnetic metal ion bound to a complex, wherein said complex comprises a chelator and a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased (i.e. increase in q value) (abstract and claim 1). The chelator is DOTA (claims 2 and 9). See also column 10-11. A blocking moiety is present, as in claims 1-9, such that the blocking moiety is associated with the chelator and which is capable of interacting with a target substance and substantially blocking the exchange of water in at least the inner coordination site of the metal ion of the metal complex (column 13, lines 11-20). The blocking moiety may comprise various components, such as one or more linker groups, etc. By "capable of interacting with a target substance", it is meant that the blocking moiety has an affinity for the target substance, such that the blocking moiety will stop blocking or occupying at least one coordination site of the metal ion complex when the target substance is present. Thus, the blocking moiety is blocking or occupying at least one coordination site of the metal ion in the absence of the target substance. However, in the presence

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of the target substance, the blocking moiety associates or interacts with the target substance and is released from its association with the metal ion, thus freeing at least one coordination site of the metal ion such that the rapid exchange of water can occur at this site, resulting in image enhancement. In some embodiments, the nature of the interaction is irreversible, such that the blocking moiety does not reassociate to block or occupy the coordination site; for example, when the blocking moiety comprises an enzyme substrate which is cleaved upon exposure to the target enzyme (column 13, lines 25-66). Once the target enzyme is identified or chosen, enzyme substrate blocking moieties can be designed using well known parameters of enzyme substrate specificities. When the enzyme target substance is a protease, the blocking moiety may be a peptide or polypeptide which is capable of being cleaved by the target protease. By "peptide" or "polypeptide" herein is meant a compound of about 2 to about 15 amino acid residues covalently linked by peptide bonds. Preferred embodiments utilize polypeptides from about 2 to about 8 amino acids (column 13, line 65 – column 14, line 12).

Meade does not specifically recite that the peptide cleavable by protease is an MMP active peptide. It is for this reason that Lauffer is joined.

Lauffer discloses improved diagnostic agents for Magnetic Resonance Imaging and optical imaging. In particular, MRI and optical imaging agents that allow for the sensitive detection of a specific bioactivity within a tissue are disclosed. The agents are prodrug contrast agents which are bioactivated in vivo in the presence of the specific

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bioactivity (abstract). The prodrugs must comprise three domains: an image-enhancing moiety (IEM), a modification site (MS), and a protein binding moiety (PBM) (column 4, lines 34 – 37). A preferred method of bioactivating the contrast agents includes the enzymatic cleavage of the prodrug at the MS (column 4, lines 49 – 50). When the contrast agents bind to a protein, there is a change in the IEM signal characteristic, such as a change in induced relaxation rates of water protons or a shift in one or more peaks or alteration in signal intensity in the NMR spectrum (column 6, lines 55+). The image-enhancing moiety may be gadolinium (III) chelate of DOTA (column 8, lines 43+ - column 9, line 10 or column 20, lines 55+). The protein binding moiety (PBM) may be a peptide (column 10, line 8). The modification site (MS) is a domain on the prodrug which is altered by the specific bioactivity desired to be imaged, such a biotransformation, enzymatic or otherwise, may include bond cleavage, etc. (column 15, lines 18 – 29). Preferred MSs are those which are altered by matrix metalloproteinases (MMPs), including MMP-7 (column 18, lines 14 – 37). Another particular example is that of MMP-1, wherein the protein binding moiety is represented by Gly-Ile-Arg-Lys and the modification site is the bond between Gly and Ile (column 19, lines 1 – 30), including enzymatic cleavage thereof (Example IV). Regarding claim 25, the agents may further comprise a masking moiety (MM) (see column 4, lines 51 – 56 and column 5, line 1), which may include a carbohydrate moiety (column 20, line 18).

It would have been obvious to one of ordinary skill in the art to employ an MMP active peptide as the peptide cleavable by protease in the contrast agents of Meade comprising a blocking moiety, when the teaching of Meade is taken in view of Lauffer.

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While Meade teaches that a blocking moiety cleavable by a protease may be present on his contrast agents, MMP proteases are not specifically recited. However, Lauffer teaches that matrix metalloproteinases (MMPs) are enzymes which exhibit high bioactivity in the extracellular space, a tissue compartment which is easily accessible to contrast agents. Furthermore, MMP activity is altered by many diseases. To varying degrees, members of the MMP family are linked to the following diseases: cancer (especially in the degradation of extracellular matrix prior to metastases), atherosclerosis myocardial infarction or unstable angina), rheumatoid arthritis, etc. In the case where the targeted bioactivity is the enzymatic activity expressed by MMP-1, a matrix metalloproteinase which is elevated in certain inflammatory diseases, a preferred MS is the carbon-nitrogen amide bond linking the amino acids glycine (Gly) and isoleucine (Ile). MMP-7 is also disclosed (see column 18, lines 14+). Therefore, one of ordinary skill in the art would have been motivated to employ an MMP active peptide as a protease target in the blocking moiety of the compounds of Meade, since Lauffer teaches MMP to be associated with a variety of diseases, and that one could use the compounds for detection of MMP enzymatic activity. One would have had a reasonable expectation of success in doing so because both Meade and Lauffer are drawn to activatable MRI contrast agents comprising a chelator and a target site activatable by a biological target, and Lauffer exemplifies such cleavage activity by an MMP enzyme towards an MMP peptide substrate.

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Claims 19 – 22, 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade *et al.* (US 5,707,605) in view of Lauffer *et al.* (US 6,709,646) in further view of Netzel-Arnett *et al.* (*Biochem.*, 1993, 32, p. 6427 – 6432).

The rejection over Meade in view of Lauffer is applied as above.

Meade and Lauffer teach activatable contrast agents, as set forth above, but do not specifically teach that the cleavable blocking moiety, or protein binding moiety and modification site, are a peptide sequence including $X_1-(Y_1)_n\text{-Ala-Leu}-(Y_2)_m$, where Y_1 and Y_2 are independently amino acid moieties, and n and m are independently an integer from 0 to 5, or applicant's elected species SEQ. ID. No. 4 (Pro-Met-Ala-Leu-Trp-Met-Arg). However, Lauffer teaches that a preferred modification site is that which is altered by matrix metalloproteinases (MMPs), including MMP-7, or matrilysin (column 18, lines 14 – 37).

Netzel-Arnett discloses that MMP (matrix metalloproteinases) are a family of enzymes that are believed to play a leading role in both the normal turnover and pathological destruction of the extracellular matrix (page 6427). Matrilysin, or PUMP-1 (i.e. MMP-7) hydrolyzes proteoglycans, fibronectin, laminin, gelatin and other substrates (page 6428, left column). The homologous MMP family of proteinases can exhibit diversity in their protein substrate specificity. Netzel-Arnett studied the sequence specificity of PUMP and two other proteinases (HFC and HNC) in order to elucidate the contribution of sequence specificity to protein specificity, important to the design of optimized synthetic substrates and inhibitors (page 6428, left column). Peptides 1 – 58 were prepared and compared to a reference octapeptide which is modeled after the

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collagenase cleavage site of calf/chick alpha1(1) chain of collagen. Kinetic parameters for the hydrolysis of these peptides by PUMP, HFG and HNG were determined (page 6428). PUMP exhibits a strong preference for Leu in subsite P₁' (page 6431, left column and Table 5). Synthetic substrates were prepared and tagged with a fluorescent Trp residue in subsite P₂', a dinitrophenyl quenching group on the N-terminus, and an Arg residue for enhanced solubility in subsite P₄'. Quenching of the Trp fluorescence by the DNP group in the intact peptide is relieved on hydrolysis of the P₁-P₁' bond for a continuously recording fluorescent assay (page 6431, left column). A good candidate substrate for PUMP is DNP-Pro-Met-Ala-Leu-Trp-Met-Arg.

Netzel-Arnett teaches the PUMP, or MMP-7, substrate Pro-Met-Ala-Leu-Trp-Met-Arg to be conjugated to an alternative imaging moiety, a fluorescent moiety (DNP), rather than an MRI chelate agent.

The rejection over Meade in view of Lauffer is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the instant invention to substitute the MMP-7 substrate, Pro-Met-Ala-Leu-Trp-Met-Arg, taught by Netzel-Arnett, for the MMP-1 substrate, Gly-Ile-Arg-Lys, in the bioactivatable contrast agents of Lauffer or Meade in order to provide a suitable cleavage site for the MMP enzyme, as taught by Lauffer (see Table IV and column 19 of Lauffer). Lauffer teaches that a variety of MMP enzymes may be employed as suitable cleaving agents, including both MMP-1 and MMP-7. One would have been motivated to do so because Lauffer reasonably teaches a bioactivatable contrast agent wherein the agent comprises and MMP modification site cleavable by MMP-7, however, Lauffer does not teach an MMP-7

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specific substrate sequence, therefore one would be motivated to use the substrate taught by Netzel-Arnett as a suitable MMP-7 cleavage site. One would reasonably expect successful cleavage because Netzel-Arnett teaches such properties.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618
LHS